REMARKS

Entry of the foregoing and favorable reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R.§ 1.116, and in light of the remarks which follow are respectfully requested.

By the present amendment, claims 15, 18, 23, 24 and 25 have been amended solely to clarify the present invention. Support for the exogenous promoter appears on page 14 of the specification as filed. Support for the percentage of regression appears on page 13, lines 4 and 5 of the specification as filed. Claim 26 has been added and also has support on page 14 of the specification as filed. Applicants submit that no new matter has been added in this amendment.

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35 U.S.C. § 112

Turning now to the Official Action, claims 15-18 and 23-25 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art, at the time the application was filed, that the inventors had possession of the claimed invention. This rejection has been obviated-in-part by amendment and is being traversed in part.

Claims 15, 18 and 24 now recite that the nucleic acid sequence encoding for a cytokine is "under the control of a promoter present in said replication-defective adenoviral vector or an exogenous promoter." Support for this amendment appears on page 2, lines 20-23, in claim 1 and claim 5 as originally filed, and on page 14 of the specification as filed.

The Examiner purports that claim 25 is new matter. More specifically, the Examiner deems that the specification does not contemplate one adenoviral vector encoding both IL-2 and

GM-CSF as claimed. Applicants respectfully disagree with the Examiner for the following reasons.

On page 8, lines 9-21, relates to the construction of the recombinant adenoviruses of the present invention. More specifically, the following is stated:

> The subject matter of the invention is also a method for obtaining the recombinant adenoviruses described above, which comprises, after the actual step of construction of a vector by introduction of one or more insertion nucleic acid(s) into the genome of the initial defective adenovirus . . . (emphasis added).

See, also original claim 6 which recites that the recombinant nucleic acid contains separate inserts placed respectively under the control of separate promoters.

Furthermore, at the end of page 14, to the beginning of page 15 of the specification describes the simultaneous expression of several cytokine genes and indicates that cytokine genes are under control of different promoters and are located following one another.

The different cytokines that can be used in the present invention are described on page 4, lines 2-14, which cytokines include IL-2 and GM-CSF.

Therefore, a person skilled in the art, which is the criteria from which a written description requirement should be analyzed, would realize that the present invention does indeed contemplate the method of claim 25 using a replication-defective adenoviral vector encoding IL-2 and GM-CSF.

Indeed, it appears that the Examiner is rendering this rejection based on the requirement that a word for word disclosure of the combination of IL-2 and GM-CSF must be made in the specification. This type of conclusion is legally incorrect. As stated by the Federal Circuit in Fujikawa v. Wattanasin, 93 F.3d 1559, 1570, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996):

> *ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question (emphasis added).

Since the specification clearly describes that the replication-defective adenoviral vector can contain separate nucleic acid inserts encoding for cytokines under the control of separate promoters and since the application reasonably conveys to the person skilled in the art that IL-2 and GM-CSF are in fact cytokines, a skilled artisan would realize that from the description the inventor did know of the suitability of this combination and hence had possession of the present invention as set forth in claim 25. See also, Hoechst Celanese Corp. v. BP Chemicals Ltd., 884 F.Supp. 336, 30 USPQ2d 1833 (SD Tex. 1994).

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

35 U.S.C. § 112, First Paragraph

Claims 15-18 and 23-25 have been rejected under 35 U.S.C. § 112, first paragraph, as lacking written description. For the following reasons, this rejection is respectfully traversed.

In rendering this rejection, the Examiner purports that an adequate written description of the adenoviruses requires more than a mere statement that it is part of the invention and reference to a potential method for making it; what is required is a description of the promoters and a description of how to make the adenovirus.

The Examiner has failed to consider that on pages 9 to 15 of the specification, as well as Figure 1 provide details on how to make the defective adenoviral vector of the present invention and how and where to insert the specific cytokines described in the present invention.

The promoters are set forth on page 14 of the specification. The Examiner cannot deny that the promoters described in the present specification were promoters that were well known in the art at the time of filing the present specification.

Since the person skilled in the art at the time of filing the present invention was a person that was highly skilled, on a PhD level there is no reason the specification does not reasonably convey to the skilled artisan that the inventors had possession of a replication-defective adenoviral vector using different promoters described in the specification at the time of the filing of the application.

With respect to this rejection under written description, the Federal Circuit held in Ralston Purina Co. v. Far-Mar Co., Inc., 772 F2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) that:

> a predecessor to this court has held 'that a claim may be broader than the specific embodiment disclosed in the specification is in itself no moment.'

Furthermore, it should not be considered in a 35 U.S.C. § 112, first paragraph written description rejection that the specification contains language which corresponds identically to the language of the claims. Rather, the general meaning of the specification should be considered in light of the skilled artisan and Applicants submit that the skilled artisan is able to clearly ascertain that the inventors had possession of the claimed invention.

Therefore, withdrawal of this rejection is respectfully requested.

Claims 15-18 and 23-25 have been rejected under 35 U.S.C. § 112, first paragraph, as being unenabled. For the following reasons, this rejection is respectfully traversed.

First of all, Applicants cannot see the significance of the Examiner's comments on pages 6 to 8 of the Official Action regarding the unpredictability of targeting adenoviral vectors. Applicants submit that the claims of record recite that the pharmaceutical composition is injected into the tumor. Therefore, it appears that the Examiner's commentary with respect to vector targeting is irrelevant.

Thus, this leaves two remaining issues with respect to this rejection which are the level of various cytokines needed to inhibit tumor growth and the use of different promoters. However, prior to discussing these remaining issues in more detail, Applicants would like to make the following remarks.

It is well known historically that for enablement issues, the specification may assume that which is common and well known to persons skilled in the art. Webster Loom v. Higgins, 105 U.S. (15 Otto) 580 (1881). This legal jurisprudence remains in the law today as evidenced by the case of In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) where the courts stated that a specification in a patent need not disclose what is well known in the art.

Following the criteria set forth in In re Wands, supra, the legal issue that must be addressed concerning enablement is whether the specification teaches those skilled in the art at the time of filing of the application whether that skilled artisan can make and use the invention without undue experimentation. There are several factors that should be considered in evaluating undue experimentation which the court clearly outlined which are the following:

1. the state of the art at the time of filing the application;
2. the relative skill of those in the art at that time;
3. the nature of the invention;

4. the presence or absence of working examples in the specification;
5. the amount of guidance or direction presented in the application;
6. the quantity of experimentation necessary;
7. the predictability of the art; and
8. the breadth of the claim.

With respect to the above criteria, Applicants submit that the state of the adenoviral vector art was quite high at the time of the filing of the present application. This is evidenced by the prior art of record including Statford-Perricaudet et al., Rosenfeld et al. and Crystal et al. which references disclose the construction of various adenoviral vectors. In fact, the use of adenoviruses as vectors began around 1982, 10 years prior to the filing of the present application. For instance, the level of skill in the art around the time of filing of the present application is evidenced by Graham, Annex I, which summarizes the state of the art with respect to the construction of adenoviral vectors in 1990 and illustrates that E1 and E3 deleted vectors were well known to the skilled artisan. Therefore, Applicants submit that it was well known to the skilled artisan at the time of filing of the present application how to construct various replication-defective adenoviral vectors.

Crystal, U.S. Patent No. 6,013,638, recognized that as of October 1991, the skilled artisan knew the dosages of the adenoviral vector to be administered, as well as how to adjust dosages to a given host. These dosages and amounts were deemed to be conventional techniques at that time and obtaining such dosages would not be considered to be undue experimentation.

Russell, also of record, recognized that when various cytokines administered alone or with various cells lead to a regression of various tumors. In this regard, Annex II, Rosenberg et al. is cited with respect to the knowledge known at the time of filing of the present application with respect to the cytokine/tumor art.

Therefore, with respect to the cytokine/tumor art, Applicants submit that the state of the art with respect to dosages etc. was known to the skilled artisan at the time of filing of the present application.

Applicants also submit that the level of skill in the art was high as evidenced by Nabel, U.S. Patent No. 6,297,219. The skilled artisan knew, therefore, how to construct any viral vector, knew the amounts to be administered and knew the amounts of expression prior to June 1991. Applicants maintain the above statement since Nabel does not disclose any scientific detail of the same. Therefore, based on Nabel it can be ascertained that the skilled artisan in 1991 had a very high level of skill such as a PhD.

Thus, from the above, it is deemed the nature of the invention was such that the scientific manipulation to insert a heterologous sequence and different promoters into an adenoviral vector had a solid foundation in the art and the level of the skilled artisan was quite high. Thus, the art cannot be deemed unpredictable, as the Examiner maintains, but predictable. This predictability is again evidenced by Nabel, which does not even illustrate nor scientifically describe how any of their vector constructs for the viral vectors were made, whether they were replication defective or replication competent and yet the allowed claimed were directed to viral vectors in general. (Note that there was only a description of a murine amphotrophic β-galactosidase-transducing retroviral vector (BAG) containing neomycin genes, but no scientific detail was given therein on how to construct such a vector.)

Moreover, there were no examples in Nabel that any of the viral vectors achieved expression nor the level of expression thus achieved. This can only mean that this art is to a certain extent, with respect to expression and levels of expression, predictable and/or well known in the art prior to 1991.

With respect to the criteria concerning the content of the present application as filed, it should be noted that the present application described on pages 9 to 12 and in Figure 1 how to construct an adenoviral vector having deletions in the E1A, E1B and E3 regions and how to insert a cytokine such that expression is achieved. On page 12 it provides the skilled artisan with quantitative methods, as well as qualitative methods on how to measure the various cytokines that were expressed by the adenoviral vector. On page 14 of the present specification it provides known promoters. Thus, a person skilled in the art would know from the teachings of the specification how to insert various promoters into the replication-defective adenoviral vector and how to measure the expression thereof.

Indeed, it should be noted that the present specification filed at a later date than Nabel provides more explicit detail and guidance to the skilled artisan and the breadth of Applicants' claims are narrower than Nabel.

Applicants thus submit that it would not be undue experimentation at the time of filing the present application to construct replication-defective adenoviral vectors having deletions in the E1A, E1B and E3 regions and to comprise a cytokine under the control of a promoter present in said defective adenoviral vector or an exogenous promoter and successively attain expression of said cytokine such that can be used to treat tumors.

With respect to the quantitation of GM-CSF and the amounts, Applicants draw the Examiner's attention to pages 11 and 12 of the specification as filed wherein different methods for the expression of cytokines can be achieved. With respect to GM-CSF, the test of proliferation of TF-1 cells is disclosed. It would not be undue experimentation for the skilled artisan to use this test to determine the amounts of GM-CSF produced, especially since Annex III

(Singh et al. J. Cancer (1989)) discloses that GM-CSF at concentrations of more than 0.01 U/ml significantly augmented the effect of LAK activity induced by IL-2.

However, Applicants would like to emphasize that the expression levels of a particular cytokine is not a key issue with respect to tumor regression. Unlike gene therapy methods to correct a genetic defect, which does require stable and consistent expression at particular levels, the aim of the present invention is to transiently activate the patient's immune system. By this transient activation, the patient's own immune system responds more vigorously than usual, leading to tumor regression. Thus, strong expression at a particular level of the related cytokine at a particular level is not required to achieve tumor regression.

Furthermore, Crystal also describes that it was well within the person skilled in the art to determine dosages given to the host, since this was conventional technique back in October 1991.

With respect to the issue that the "heterologous" now "exogenous" promoters are not enabled, since the amount of expression obtained is not specified in the specification, Applicants respectfully submit that it was know in the art prior to the filing of the present application, that several of the exogenous promoters listed on page 14 of the specification can be used in conjunction with an adenoviral vector and expression of a heterologous nucleic acid sequence could be achieved. This is evidenced for example, in Annexes IV to VIII.

Again, page 11 in the specification clearly disclose various tests used to measure the levels of various cytokines.

Finally, it should be stressed that known scientific and technological information does not have to appear in the patent specification. Indeed, in the recent Federal Circuit decision of

Ajinomoto Co. Inc. v. Archer-Daniels-Midland Co., 228 F3d 1338, 1346-47, 56 USPQ2d 1332, 1338 (Fed. Cir. 2000), the Federal Circuit stated the following:

> Requiring inclusion in the patent of known scientific/technological information would add an imprecise and open-ended criterion to the context of patent specifications, could greatly enlarge the content of patent specifications and unnecessarily increase the cost of preparing and prosecuting patent applications, and could tend to obfuscate rather than highlight the contribution to which the patent is directed. A patent is not a scientific treatise, but a document that presumes a scientific readership skilled in the field of the invention.

See also, Ex parte Zechnall, 194 USPQ 462 (PTO Bd. App. 1974), wherein the Board, with respect to the written description requirement held that "minor gaps and omissions may be filled in from the prior art."

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

35 U.S.C. § 112, Second Paragraph

Claims 15-18 and 23-25 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. With respect to claims 15 and 24, this part of this rejection has been rendered moot by the claim amendments, which were modified as suggested by the Examiner.

With respect to claim 16, Applicants respectfully traverse this rejection for the following reasons.

In rendering this rejection, the Examiner purports that "an adenoviral vector cannot lack the E1A region, as in claim 15, while retaining the early promoter of the E1A region as in claim 16. The Examiner provides no scientific basis of why this cannot be achieved.

Indeed, Applicants submit that a skilled artisan knows that a promoter is 5' upstream of the coding part of the gene, but downstream of the operator. The promoter is the region to which an RNA polymerase molecule binds to initiate transcription.

The E1A region of the adenovirus is the first viral transcription unit to be expressed and is controlled by the active promoter upstream from this region. Hence, it is possible to have the E1A region deleted and still retain the upstream promoter.

Therefore, withdrawal of this rejection is respectfully requested.

35 U.S.C. § 103(a)

Claims 15-18 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Nabel (U.S. Patent No. 6,297,219) in view of Crystal (U.S. Patent No. 6,013,638). For the following reasons, this rejection is respectfully traversed.

Nabel, U.S. Patent No. 6,297,219, discloses a method of transforming cells site-specifically by introducing into a mammal by direct injection at a solid tumor various viral vectors that contain a nucleic acid sequence insert, which is expressed. When read as a whole, Nabel lists vectors including retroviral vectors, papillomaviral vectors, herepesvirus, parvovirus, adenoviral vectors and the like. There were no specific promoters disclosed in Nabel in the viral vector constructs and no constructs of an adenoviral vector which lack the E1A, E1B and E3 regions.

Crystal et al. teach the delivery into the lung of an replication-defective adenoviral vector having the E1A, E1B and E3 regions deleted and a DNA segment encoding the CFTR protein operatively linked to a promoter. However, this pharmaceutical composition disclosed therein is

for administering these vectors for the lung by local installation through a tube such as flexible bronchoscope or by aerosolization. Thus, direct injection is not foreseen in Crystal et al.

The combination of these references fails to render the present invention obvious since neither reference alone nor in combination fails to teach or even suggest that by administering the claimed pharmaceutical composition of the present invention leads to regression and complete disappearance of said tumor in 40% to 50% of patients. This regression is an unexpected result that is not disclosed, taught or suggested in Nabel or Crystal either alone or in combination.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

SUMMARY

Based on the foregoing, a favorable action in the form of a Notice of Allowance is respectfully requested and earnestly solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

15. (Twice Amended) A method for treating a tumor in a patient in need of such treatment, said method comprising injecting an effective amount of a pharmaceutical composition into said tumor wherein said pharmaceutical composition comprises:

(a) [an] a replication-defective adenoviral vector [wherein said adenoviral vector:

(i) is replication-defective and lacks] lacking the E1A, E1B and E3 regions of said adenovirus; and

[(ii)] comprises a nucleic acid sequence coding for a cytokine, under the control of a promoter present in said replication-defective adenoviral vector or an exogenous promoter [an endogenous or heterologous promoter]; and wherein said cytokine is interleukin-2 or gamma-interferon; and

(b) a pharmaceutically acceptable vehicle wherein said pharmaceutical composition leads to regression of said tumor in at least 40% to 50% of patients.

18. (Twice Amended) The method according to Claim 15, wherein said nucleic acid sequence coding for said cytokine is under the control of said [heterologous promoter] exogenous promoter.

23. (Once Amended) The method according to Claim 18, wherein said [heterologous] promoter is the promoter of the IE gene of cytomegalovirus.

24. (Once Amended) A method for treating a tumor in a patient in need of such treatment, said method comprising injecting an effective amount of a pharmaceutical composition wherein said pharmaceutical composition comprises:

(a) [an] a replication-defective adenoviral vector [wherein said adenoviral vector;

(i) is replication-defective and lacks] lacking the E1A, E1B and E3 regions of said adenovirus; and

[(ii)] comprises a nucleic acid sequence coding for a cytokine, under the control of a promoter present in said replication-defective adenoviral vector or an exogenous promoter [an endogenous or heterologous promoter]; and wherein said cytokine is GM-CSF, and

(b) a pharmaceutically acceptable vehicle.

25. (Once Amended) The method according to Claim 24, wherein said adenoviral vector further comprises a nucleic acid sequence coding for an interleukin-2 under the control of [an endogenous or heterologous promoter] a promoter present in said replication-defective adenoviral vector or an exogenous promoter and wherein said interleukin-2 under the control of said [endogenous or heterologous promoter] promoter present in said replication-defective adenoviral vector or said exogenous promoter is placed after said nucleic acid sequence coding for a cytokine in said adenoviral vector.